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Gina N. Shishima

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Susan Lindquist

Serial No.: 09/207,649

Filed: December 8, 1998

For: METHODS FOR IDENTIFYING FACTORS THAT CONTROL THE FOLDING OF AMYLOID PROTEINS OF DIVERSE ORIGIN

Group Art Unit: 1647

Examiner: S. Turner

Atty. Dkt. No.: ARCD-278

REPLY BRIEF

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REPLY BRIEF

Board of Patent Appeals and Interferences
U. S. Patent and Trademark Office
Washington, D.C. 20231

This Reply Brief is filed in response to the Examiner's Answer mailed on February 21, 2003, regarding the above-captioned application. It is believed that no fee is due; however, should any other fees under 37 C.F.R §§ 1.16 to 1.21 be deemed necessary for any reason relating to the enclosed materials, the Commissioner is hereby authorized to deduct said fees from Fulbright & Jaworski L.L.P. Deposit Account No. 50-1212/ARCD:278.

Appellant also includes herewith a Request for Oral Argument, along with the requisite fee.

I. ARGUMENT

Appellant relies on the arguments set forth in the Appeal Brief and adds the following comments with respect to the Examiner's Answer ("Answer").

A. The Examiner Has Not Fulfilled Her Burden in Showing that Hughes et al. Anticipates the Claimed Invention

Appellant emphasizes again that the Hughes *et al.* ("Hughes") reference itself clearly shows that an association of two monomers does not constitute "aggregation," as recited in the rejected claims.

The Examiner argues that Hughes "makes clear that the study of issue is designed to function as an indication of aggregate formation." Answer at page 13. It cites the following portion of Hughes:

> The findings presented in this paper suggest that the two hybrid system can be used to study the interaction of Abeta [sic] monomers and to define the peptide sequence that may be important in nucleation-dependent aggregation.

Hughes at page 2070. The Answer also cites Hughes as stating that "the slow and thermodynamically unfavorable interactions between individual monomers may be the rate-limiting step in aggregation." It concludes, "Thus, in contrast to Appellant's interpretation the Examiner notes that these passages apparently refer to the earliest forms of aggregation as that between two monomers." Answer at page 13.

Appellant cited that same first passage in the Appeal Brief, relying on it to show the tentativeness the Hughes' authors exhibited when discussing how monomer interactions may provide insight into nucleation-dependent aggregation. The authors specifically said those interactions "may be" important to aggregation, as opposed to saying such interactions constituted aggregation or were important. Moreover, the Examiner herself is tentative in her conclusions because she says that these passages "***apparently*** refer" to the earliest forms of aggregation. This is not sufficient to meet the threshold burden on the examiner to show that a reference anticipates the claimed invention because the Examiner has not shown that the reference teaches all of the elements of the rejected claims.

Also, as discussed in the Appeal Brief, the Hughes reference itself clearly differentiates monomer formation from a developed nucleus. The statements quoted above indicate that nucleation precedes aggregation and that aggregation is dependent on nucleation. In Fig. 1 of Hughes, it distinguishes the monomer association from the already formed nucleus. It does not show the monomer association to be a nucleus itself, and instead, the figure legend indicates that the association is "an essential first step in the nucleation event leading to fibril formation." However, achieving the first step does not mean that the final product is achieved. For example, cleaving a plasmid with a restriction enzyme to create a place to ligate an insert may be a first and necessary step in making a new vector, but having done that does not mean the vector with the insert has been produced at that point. Similarly, Fig. 1 illustrates that other events are required in addition to a single monomer association to achieve a nucleus.

The Examiner also argues that Appellant and the art "appear to recognize that monomer interaction forms an aggregate as such is measured via circular dichroism, seeded assays or nucleation-dependent assays," but she cites no evidence to support that these assays could recognize monomer interactions. Furthermore, as discussed in the Appeal Brief, the two-hybrid assay of Hughes cannot be an assay for aggregate formation, because that assay would actually fail to show anything if a nucleus is formed. As Fig. 1 makes clear, the assay is dependent on only monomer associations. The Hughes' authors performed the assay to ensure that nuclei, as shown in Fig. 1, would not form because they were able to observe expression of the reporter gene, β-Gal, which would not have occurred if a nucleus comprised of bait and prey had been formed.

Since the Hughes *et al.* reference does not teach or even suggest all of the claim limitations in Appellant's claimed invention, it does not anticipate or render obvious the presently claimed invention. Accordingly, Appellant respectfully requests that the rejection of

claims 1, 3, 7-20, and 22 under 35 U.S.C. § 102(b) as being anticipated by Hughes *et al.* be withdrawn.

B. The Examiner's Understanding of the Term "Chimeric" Is Unsupported, and Consequently, Cordell *et al.* Does Not Anticipate the Claims

The Examiner states that Appellant's definition of "chimeric" includes the substituted mutants of Cordell *et al.*. This contention is unsupported.

As discussed in the Appeal Brief, the specification defines "chimeric protein" to mean "the protein comprises *polypeptides* that do not naturally occur together in a single protein unit." Specification at page 5, lines 26-27. Appellant's specification uses the term "polypeptides" and it is also used in the plural form, so single amino acid substitutions are excluded.

The Examiner erroneously contends that "Appellants appear to argue that a modified protein cannot be considered to be two different peptides combined to form a non-naturally occurring polypeptide." Answer at page 14. A chimeric polypeptide can comprise two different peptides. However, a chimeric polypeptide is not a polypeptide that has a single amino acid substitution.

Moreover, the Federal Circuit has emphasized that the "terms used in the claims bear a 'heavy presumption' that they mean what they say and have the ordinary meaning that would be attributed to those words by persons skilled in the relevant art." *Texas Digital Sys., Inc. v. Telegenix, Inc.*, 308 F.3d 1193, 1203 (Fed. Cir. 2002). To this end, the Examiner has not cited *a single reference* to support her position that a person of ordinary skill in the art would interpret "chimeric protein" to mean any polypeptide with any changes in it. Appellant contends this has not been done because such a reference does not exist. In fact, a skilled artisan would understand that term to mean what the Appellant has defined in the specification. The Encyclopedia of Molecular Biology (1993) supports this understanding, defining "chimeric antibody" as "an antibody molecule that contains structural elements from two or more different antibody

molecules, often from different animal species." It would be readily understood that a chimeric polypeptide was a polypeptide molecule that contains structural elements from two or more different polypeptide molecules. It has been a longstanding rule that "dictionaries, encyclopedias, and treatises" are "objective resources that serve as reliable sources of information on the established meanings that would have been attributed to the terms of the claims by those of skill in the art." *Id.* at 1202-03; *see also* MPEP §2173.05(a) ("It is appropriate to compare the meaning of terms given in technical dictionaries in order to ascertain the accepted meaning of a term in the art. *In re Barr*, 444 F.2d 588 (C.C.P.A. 1971)).

The specification fully supports this definition of "chimeric." It states:

> Preferred chimeric proteins comprises at least the N-terminal domain of Sup35. This domain has been found to form aggregates in yeast and *in vitro* and is capable of causing the aggregation of chimeric proteins comprising this domain. Other preferred chimeric proteins include comprises at least an aggregate forming domain of a mammalian amyloid polypeptide, such as at least amino acids 1-42 of the β-amyloid protein or at least the aggregate forming domain of PrP. In an important embodiment, the chimeric protein comprises Sup35 in which the N-terminal domain has been replaced by amino acids 1-42 of β-amyloid protein. In other embodiments, the chimeric protein comprises at least an aggregate forming domain of an aggregate-prone amyloid protein operably attached to a detectable marker protein.

Specification at page 5, line 29 to page 6, line 9.

Appellant further notes that the term "chimeric polypeptide" would be understood by a person of ordinary skill in the art to include a fusion protein or polypeptide. Typically, fusion proteins involve fusing a portion of one polypeptide to the end of another polypeptide, as is shown in the Hughes reference. In the Hughes reference, [f]usion proteins were created by linking the Aβ fragment to the LexA DNA-binding domain (bait) and also to the B42 transactivation domain (prey)." Hughes Abstract and Fig. 1. The application fully contemplates such fusion proteins, as demonstrated in the quoted portion of the specification (above) in which

amino acids 1-42 of β-amyloid protein replace the N-terminal domain of Sup35. Such a protein is understood to be a fusion protein and an example of a chimeric polypeptide.

Furthermore, Cordell *et al.* ("Cordell") states:

> As mentioned above, these genes may be natural, synthetic or combinations thereof. When preparing a synthetic nucleotide sequence, it may be desirable to modify the natural amyloid nucleic acid sequence. For example, it will often be preferred to use codons which are preferentially recognized by the desired host. In some instances, it may be desirable to further alter the nucleotide sequence, either synthetic or natural, to create or remove restriction sites to, for example, enhance insertion of the gene sequence into convenient expression vectors or to substitute one or more amino acids in the resulting polypeptide to increase stability.

Cordell at page 8, lines 20-31. This passage does not indicate or suggest chimeric polypeptides, which is a recited element of the claimed invention.

Accordingly, for the foregoing reasons and the arguments articulated in their Appeal Brief, Appellant respectfully requests that the rejection of claims 1, 3, 7-20, 22, and 37 under 35 U.S.C. § 102(b) as being anticipated by Cordell be withdrawn.

C. Findeis *et al.* Does Not Teach a Screening Assay in Yeast

The Answer argues that Findeis *et al.* ("Findeis") "does teach expression of the peptide modulators via recombinant DNA technology in yeast." Answer at page 15. However, the issue is not simply whether Findeis mentions expression in yeast, but whether it teaches the claimed invention, which is directed to a screening method to be performed in yeast.

Findeis is insufficient. It does not state that the claimed screening method can be done in yeast. It merely mentions that peptides can be expressed in yeast. The only statements the Findeis patent makes about yeast are the following:

> The recombinant expression vectors of the invention can be designed for expression of peptide compounds in prokaryotic and eukaryotic cells. For example, peptide compounds can be expressed in bacterial cells, such as

> *E. coli*, insect cells (using baculovirus expression vectors), yeast cells or mammalian cells. Col. 38, lines 1-6.
>
> Examples of vectors for expression in yeast *S. cerevisiae* include pYepSec1, pMFa, pJRY88, and pYES2. Col. 38, lines 12-17 (citations omitted).
>
> A recombinant expression vector comprising a nucleic acid encoding a peptide compound that alters aggregation of natural β-AP can be introduced into a host cell to thereby produce the peptide compound in the host cell. Accordingly, the invention also provides host cells containing the recombinant expression vectors of the invention. . . . For example, a peptide compound may be expressed in bacterial cells such as *E. coli*, insect cells, yeast or mammalian cells. Preferably, the peptide compound is expressed in mammalian cells. Col. 38, lines 48-53 and lines 62-65.

There is no indication in the patent that any screening method of the claimed invention should be or even could be performed in a yeast cell. Accordingly, Appellant respectfully requests that the rejection of claims 1, 3, 7, 12-13, 17-18, and 37 under 35 U.S.C. § 102(e) as being anticipated by Findeis be withdrawn.

D. No Evidence That Claim Terms Are Repugnant or That Claims Are Indefinite

The Examiner maintains that certain terms are repugnant to their art accepted meaning and/or are indefinite, rendering the claims indefinite. These terms include "amyloid protein," "amyloid peptide," "aggregated amyloid formation," "aggregation," and "chimeric."

Claim 1 recites:

> A method of identifying a candidate substance that inhibits the aggregation of a mammalian aggregate-prone amyloid protein, comprising:
>
> (a) contacting a yeast cell that expresses a chimeric aggregate-prone amyloid protein comprising a mammalian aggregate-prone amyloid peptide with said candidate substance under conditions effective to allow aggregated amyloid formation; and
>
> (b) determining the ability of said candidate substance to inhibit the aggregation of the aggregate-prone amyloid protein.

A person of ordinary skill in the art would understand that the yeast cell recited in claim 1 expresses an aggregate-prone amyloid protein that is 1) chimeric and 2) includes at least the part of an aggregate-prone amyloid polypeptide from a mammal that can aggregate to form an amyloid or amyloid-like deposit. Claim 3 makes clear that PrP and β amyloid are specific embodiments from which element 2) can be satisfied. The Examiner contends the terms "polypeptide" and "peptide" are unclear, but has not provided any reference to support a contention that a person of ordinary skill in the art would not understand the scope of the claims because of those terms ***and*** has never suggested an amendment that would address her concerns, as is encouraged in MPEP §2173.02.

As for the terms "aggregated amyloid formation" and "aggregation," it appears from the Answer that those terms can be understood readily. The Answer states that for the term "aggregation," it "could indicate insolubility, spectral shift, self-binding or binding to an alternative peptide." Answer at page 16. The Examiner further argues that the art recognizes various forms of "amyloid fibril aggregation," and she cites four articles of record, but never identifies where in those references the "various forms" are discussed nor does she indicate how they differ from one another. In fact, these references discuss the same or similar proteins that are recognized as capable of forming amyloid deposits. Moreover, even if different forms were identified in those papers, there is no reason that the term could not be construed to include all of those forms. Such a construction does not make the term indefinite because as the cited references make clear, the terms "amyloid" and "aggregation" are art-accepted and art-understood terms. For example, the title of the Findeis patent is "Aβ Peptides That Modulate β-Amyloid Aggregation" and the first two sentences of the Abstract states: "Compounds that modulate the aggregation of amyloidogenic proteins or peptides are disclosed. The modulators of the invention can promote amyloid aggregation or, more preferably, inhibit natural amyloid

aggregation." Again, there is nothing specifically cited by the Examiner to indicate a person of ordinary skill in the art would not be able to understand "aggregation" or "aggregated amyloid formation," nor has she identified a better term that is supported by the specification.

The Answer also argues about the term "chimeric." The discussion about this term is discussed earlier with respect to the art rejection. Appellants emphasize that a person of ordinary skill in the art would readily understand the term, and consequently, the scope of the claim, in light of the specification, the ordinary meaning of the term, and the prosecution history of this application.

Accordingly, Appellant respectfully requests that the rejection of claims 7-11 under 35 U.S.C. § 112, second paragraph be withdrawn.

II. CONCLUSION

Appellant has provided arguments that overcome the pending rejections. Appellant respectfully submits that the Office Action's conclusions that the claims should be rejected are unwarranted. It is therefore requested that the Board overturn the Action's rejections.

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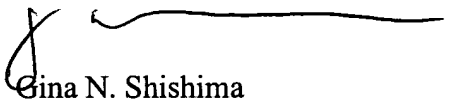
Respectfully Submitted,



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